Complications of Parathyroid Surgery

46

Nicolas Ávalos Jobet and Mauricio A. Moreno

Contents

N.Á. Jobet, M.D., F.A.C.S.
Head and Neck Surgery Division, Department of General Surgery, Chilean Air Force Hospital, Chilean Head and Neck Institute, Avenida Las Condes N° 8631, Las Condes, Santiago, Chile
e-mail: nicolasaval@gmail.com

M.A. Moreno, M.D. (✉)
Department of Otolaryngology—Head and Neck Surgery, University of Arkansas for Medical Sciences, 4301 W. Markham Street #543, Little Rock, AR 72205-1709, USA
e-mail: mamoreno@uams.edu

Introduction

Given the anatomical, functional, and vascular characteristics of the parathyroid glands, surgical intervention of these structures has an inherent risk that, while seldom life-threatening, can have devastating and life-long consequents for the patient. It is important to highlight that most of the complications associated with parathyroidectomy are avoidable with a thorough understanding of the anatomy, appropriate patient selection, and meticulous surgical technique. The risk profile of parathyroid surgery varies significantly depending on the disease status, previous interventions, and patient comorbidities; an experienced surgeon should be able to take all of these variables into account, and convey a proper estimation of the individualized risk assessment to the patient.

The reported procedure-specific, long-term morbidity rate associated with primary parathyroidectomy is only 1 % [1]. However, the risk of complications increases exponentially in the context of reoperative surgery, where it has been reported as 27–54 % [2–5], while in the geriatric population where it ranges from 4 to 10 % [6].

Mortality from elective parathyroid surgery is extremely rare, approaching 0 % in the vast majority of contemporary reports [1]. It is, however, considerably higher in the geriatric population, where it consistently approaches 1 % [7–9],

B.C. Stack, Jr., D.L. Bodenner (eds.), *Medical and Surgical Treatment of Parathyroid Diseases*,
DOI 10.1007/978-3-319-26794-4_46

and has been reported to be as high as 10 % [6]. The elevated mortality rate in this subset of patients appears to be related to presence of medical comorbidities, and not to a higher rate of surgical complications [6–9].

Below we describe the most common complications of parathyroid surgery and discuss their etiology, management, and most importantly, the technical considerations necessary to avoid them.

Postoperative Hypocalcemia

Hypocalcemia is one of the most common complications after parathyroid surgery. Depending on its temporal progression, postoperative hypocalcemia can be defined as transient or permanent, depending on if it extends beyond 12 months postoperatively [10]. While hypocalcemia and hypoparathyroidism are used indistinctly in the literature they are not necessarily the same, and it is possible to have hypocalcemia with normal PTH levels, and symptoms of hypocalcemia in eucalcemic patients [10]. The incidence of transient postoperative hypocalcemia among patients treated for primary hyperparathyroidism is 15–30 % [1], but recent series report lower incidences. Miccoli et al. report a 2.7 % incidence in patients treated with video-assisted parathyroidectomy [11], while in a series of 656 patients Udelsman reports an incidence of only 0.5 % [12]. A randomized trial comparing bilateral neck exploration vs. minimally invasive parathyroid surgery (MIPS) showed that while transient postoperative hypocalcemia was more frequent with open exploration, there were no differences in symptomatic or permanent hypocalcemia [13].

Overall, at 0.1 % the risk of permanent hypocalcemia is extremely low for patients undergoing primary parathyroid surgery; [14] however, it rises exponentially in the context of reoperative parathyroidectomy where is as high as 15–30 % [10]. The individual risk for postoperative hypocalcemia is in direct correlation with the activity of the parathyroid adenoma and its functional impact. Patients with preoperative bone pain, elevated alkaline phosphatases and serum PTH greater than 500 pg/ml have a significantly higher risk of postoperative hypocalcemia and in extreme cases, even risk of hungry bone syndrome. Transient hypocalcemia is routinely managed with calcium supplementation in an outpatient basis, while permanent hypocalcemia requires close follow up, appropriate counseling and specialized management.

Two main etiopathogenic mechanisms are behind the development of postoperative hypocalcemia. First, the presence of a parathyroid adenoma functionally suppresses normal parathyroid glands. This suppression, in combination with the short half-life of PTH (3–5 min), can precipitate transient hypocalcemia after surgical ablation of the adenomatous gland, especially in patients preoperative PTH well above the normal range. In this setting, hypocalcemia is unavoidable, as it truly represents a homeostatic adjustment secondary to abrupt changes in serum PTH levels. The second mechanism is surgical manipulation of the parathyroid glands. In this setting, trauma to the gland's delicate vascular pedicle results in vasospasm and transient ischemia, which clinically presents as a temporary functional impairment also known as "parathyroid stunning." The degree and extension of the parathyroid dysfunction is proportional to the level of trauma; complete devascularization of the glands will invariably lead to permanent loss of function and depending on the number of glands affected, potentially to permanent hypoparathyroidism.

Since surgical trauma is preventable, the importance of thorough knowledge of the vascular anatomy, meticulous dissection, and bloodless surgical field cannot be overemphasized. From the vascular standpoint, in most cases the blood supply to the superior and inferior parathyroid gland comes from the inferior thyroid artery [15], although the superior gland may occasionally receive vascularization from the superior thyroid vessels (Fig. 46.1). In order to preserve the vascular integrity of the parathyroids, the same surgical principles used for a thyroid surgery should be applied: maintaining the dissection plane at the level of the thyroid capsule, ligating branches of the inferior thyroid artery as distally as possible, and performing a controlled ligation of the superior thyroid vessels, after ruling out the presence of direct contributions to the superior parathyroid gland [15, 16].

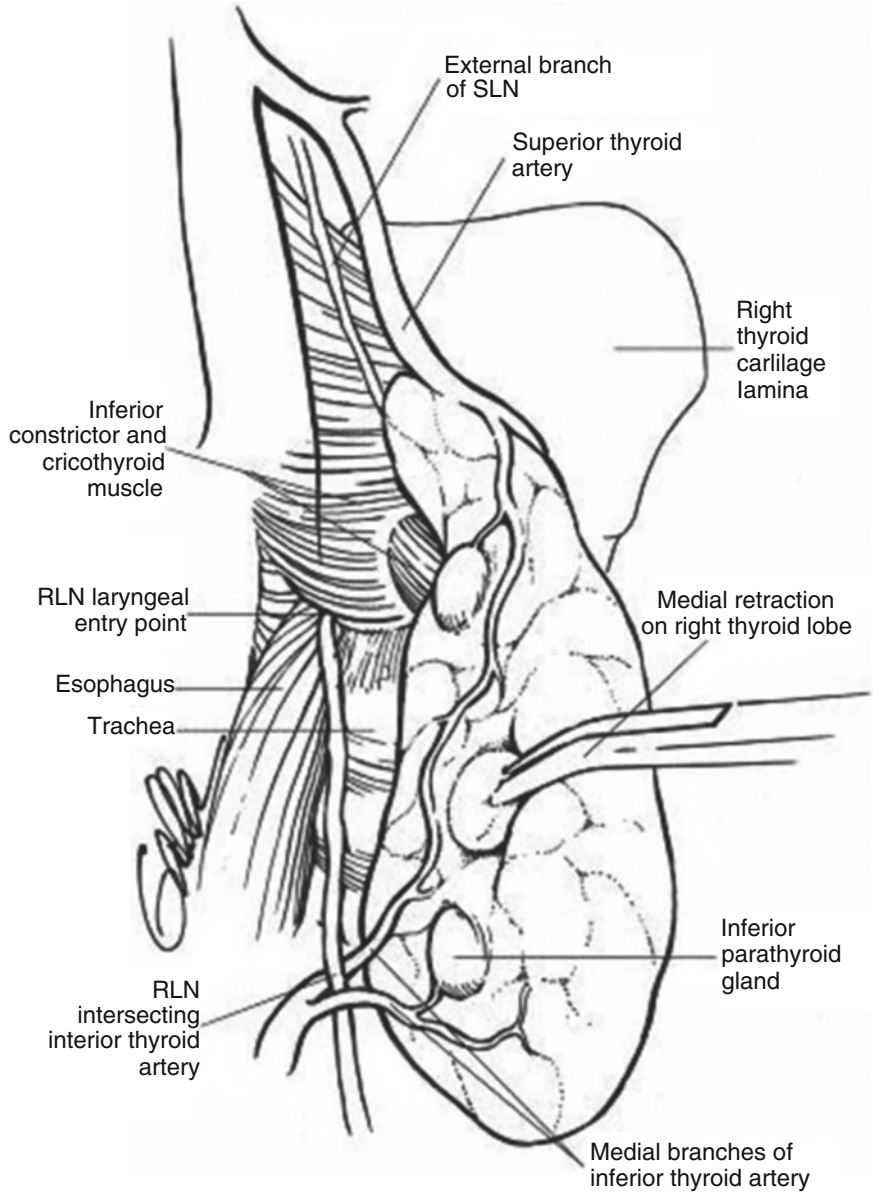

Fig. 46.1 Vascular supply of the parathyroid glands and relationship with the thyroid gland and recurrent laryngeal nerve. Surgery of the Thyroid and Parathyroid Glands Edition 2, Greg W. Randolph, editor, Elsevier Saunders Philadelphia 2012

Recurrent Laryngeal Nerve Injury

The risk injury to the recurrent laryngeal nerve (RLN) is inherent to any surgical procedure involving the central compartment of the neck. For surgeons, the best strategy to prevent nerve injury is to be familiar with the normal anatomy—including its variations—and most importantly, the anatomical relationships of the RLN and parathyroid glands.

Both the right and left RLN originate as braches of the vagus nerve in the thorax. In the right side the recurrent nerve emerges posteriorly

as the vagus crosses the subclavian artery, while in the left side it does so as the vagus crosses over the aortic arch. After circumventing subclavian artery and aortic arch and respectively, both nerves ascend along the tracheoesophageal groove towards the laryngeal inlet. In contrast with the near-vertical path of the left RLN, the right nerve has a more oblique course, explained by its relatively lateral point of inflection. As the RLN ascends in the neck, it becomes intimately related to the thyroid gland and to the inferior thyroid artery (ITA). In roughly 65–70 % of the cases the nerve courses deep to ITA, in 20–25 % of the cases is superficial to the vessel, and it courses between the ITA branches in approximately 5 % of the cases [17], as shown in Fig. 46.2. In light of variable relationship between the RLN and the ITA, we recommend against using this vessel as the sole anatomical landmark for the identification of the nerve. Also, an anatomical study suggests that the ITA is absent in 6 % of the population [18], further underscoring this concept.

During its cervical course, the RLN branches prior to its point of entry into the larynx in 20–65 % of the cases [19–21], commonly in an anterior and a posterior branch. In this setting, most authors agree that anterior branch contains the majority of the motor fibers—both abductor and adductor—while the posterior branch is predominantly sensory [22]. The surgeon must be able to promptly identify the presence of RLN branching during the course of the dissection, as this anatomical variation has been associated with a twofold increase in the risk of RLN injury [23].

Intraoperative electrophysiologic recurrent laryngeal nerve monitoring (EMG) can be a useful tool in the identification of the RLN, particularly in challenging situations such as reoperative parathyroidectomy. While nerve monitoring has not proven to decrease the incidence of RLN injury, it has a well-documented prognostic role. In a recent study involving almost 1000 at-risk nerves, Genther et al. report a sensitivity of 95.5 % and a specificity of 99.2 % of EMG for identification of immediate postoperative vocal cord paralysis in patients undergoing thyroid- or parathyroidectomy [24].

Is important for the surgeon to clearly assess and document the patient's vocal status pre- and postoperatively, as patients with a well-compensated vocal cord paresis or paralysis can present with a normal voice. The author's preference is to visualize the larynx through an indirect laryngoscopy preoperatively in all patients as this is a noninvasive procedure that allows for documentation of the vocal cord function, and serves as a reference for future examinations. If the patient presents with any vocal impairment and/or the vocal cords can't be properly visualized with this technique, a flexible fiberoptic laryngoscopy should be considered [22]. The same approach is recommended postoperatively, where functional

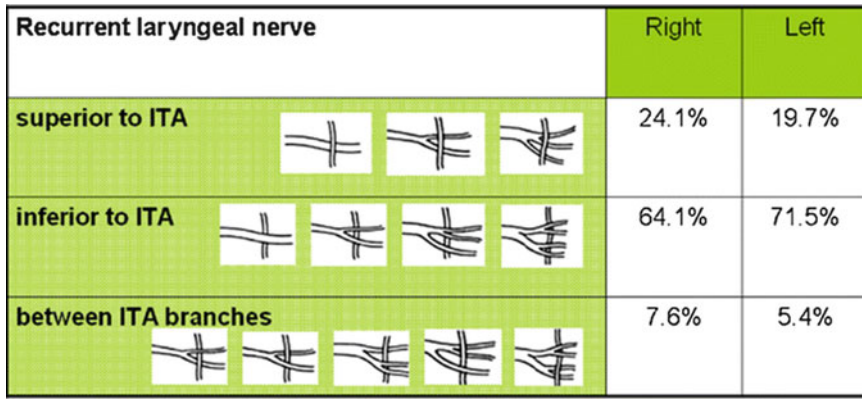

Fig. 46.2 Distribution of the anatomical relationship between the recurrent laryngeal nerve and the inferior thyroid artery Makay et al. [17]

manifestations of an acute RLN injury are not always obvious and may take some time to develop. Immediately after denervation, the balance of adductor and abductor musculature causes the vocal cord to migrate to a paramedian position. In this location the contralateral vocal cord may often compensate for the deficit, resulting mild symptomatology. In this context, patients often complain of a "weak" or raspy voice which not uncommonly is attributed to endotracheal intubation [25]. As the cord lateralizes—over the period of days to weeks—progressive hoarseness and vocal fatigue ensue, and patients develop a characteristic "breathy" voice that reflects the presence of an uncompensated glottic gap.

Postoperatively, surgeons should maintain a high index of suspicion for RLN injury. Should a patient present with a vocal cord paralysis, he or she should be counseled and promptly referred for specialized care. The chances for spontaneous recovery of the nerve function greatly depend on the mechanism and severity of the injury. Neurapraxia usually results from traction- or thermal injury to the nerve, and it has a better chance of spontaneous recovery than those cases where the nerve was transected. The treatment of unilateral vocal cord paralysis includes operative and nonoperative management and depends on the functional impact, patient's vocal needs, and estimated changes for spontaneous recovery. Vocal cord medialization or thyroplasty are commonly performed in patients in whom recovery not anticipated based on the temporal profile and/or electromyographic findings.

Bilateral vocal cord paralysis is an extremely rare occurrence in the context of parathyroidectomy, but still worth noting given its life-threatening implications. In this scenario, both vocal cords migrate to paramedian position causing an acute airway obstruction that clinically presents as stridor. This usually becomes obvious as soon as the patient is extubated, but may go unrecognized until the patient is in the recovery room. Bilateral vocal cord paralysis is a medical emergency, and the goal in this setting is to promptly secure the airway. This is most commonly achieved through endotracheal intubation, but the surgical team should ready to establish a surgical airway.

Is important to recognize that in 0.3–4% of the cases the nerve has no nonrecurrent course and originates directly as a cervical branch of the vagus nerve, without entering the mediastinum [26] (Fig. 46.3). This anatomical variation is explained by an embryological involution of the fourth aortic

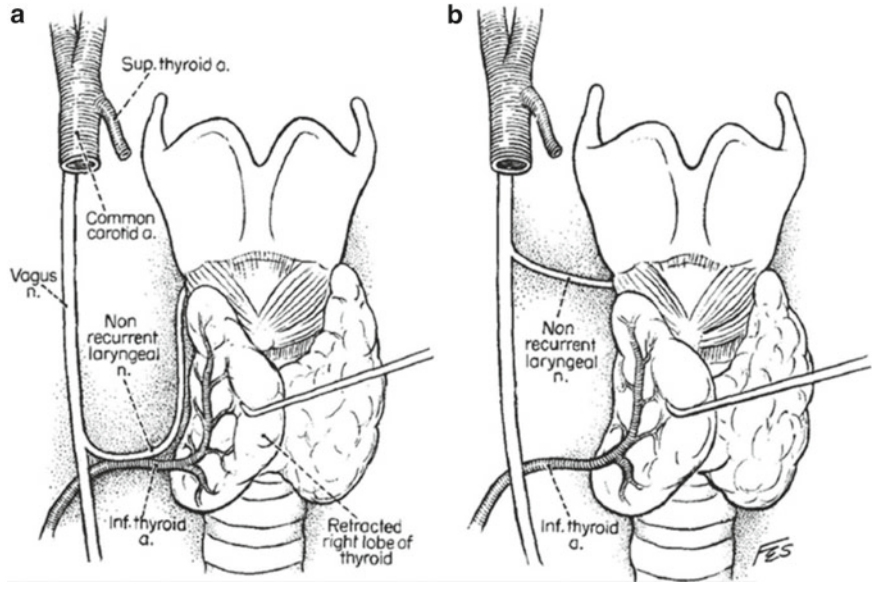

Fig. 46.3 Variations of nonrecurrent recurrent laryngeal nerve. Surgery of the Thyroid and Parathyroid Glands Edition 2, Greg W. Randolph, editor, Elsevier Saunders Philadelphia 2012

arch which causes the subclavian artery to arise from directly from the aortic arch [27]. In these cases the right subclavian artery commonly has a retropharyngeal course (*arteria lusoria*) where it can cause organic esophageal obstruction that presents as dysphagia lusoria [28]. Left-sided nonrecurrent laryngeal nerves are extremely rare. They occur only in the context of situs inversus and patients present with a corresponding left retropharyngeal subclavian artery [28].

Overall, the risk of recurrent laryngeal nerve injury after parathyroidectomy has been reported to be below 1 % in most series regardless of the type of surgical approach [6, 11, 12, 14, 29, 30]. Few studies have directly compared the risk of RLN injury between surgical techniques. In a series of 1300 patients treated at a teaching hospital for benign primary hyperparathyroidism, Karakas et al. [31] reported an incidence of permanent vocal cord paralysis of 0.4 % for minimally invasive parathyroidectomies vs. 2 % for bilateral open exploration. However, other series have found comparable rates of RLN injury between neck exploration (0.7 %) and MIP (0.8 %) [12], suggesting that the surgeon's experience might play a more significant role than the surgical approach utilized.

In a reoperative setting the presence of scar tissue, loss of anatomical landmarks and frequent need for more extensive dissection inherently increase the risk of RLN injury. A recent study describes a 9 % permanent vocal cord paralysis in patients undergoing revision surgery for persistent or recurrent hyperparathyroidism [3], almost a tenfold increase over the reported rate for primary surgery. Preoperative counseling, baseline laryngeal examination, and intraoperative EMG laryngeal monitoring should be considered in all patients undergoing a revision parathyroidectomy.

Persistent and Recurrent Hyperparathyroidism

Biochemical cure is defined as eucalcemia and normalization of serum PTH at 6 months postoperatively. Persistent hyperparathyroidism is defined as a PTH elevation within 6 months of surgery, while recurrent hyperparathyroidism is defined as PTH elevation beyond 6 months postoperatively, following a period of normalization. Since most of the surgical failures are preventable, it is worth discussing the process of patient selection and technical aspects of the surgery.

Primary hyperparathyroidism is caused by a single adenoma in 85–95 % of the cases [32–36], and a second adenoma is present in 3–5 % of the patients [37]. The incidence of 4-gland hyperplasia ranges between 2 and 6 %, but has been reported to be as high as 15 % [35, 36]. Parathyroid localization allows the surgeons to differentiate single vs. multigland disease preoperatively. Those patients with localizing disease (80–90 %) are candidates for a unilateral (minimally invasive) parathyroidectomy. The options for preoperative localization include: neck ultrasound, Sestamibi-SPECT, CT scan with and without contrast (4DCT), and magnetic resonance imaging (MRI). These test are not mutually exclusive and can be combined in an attempt to increase the accuracy of localization. Sestamibi-SPECT is by far the most commonly utilized, and currently considered as part of the standard of care. However, 4DCT has been rapidly adopted as it has demonstrated better sensitivity than Sestamibi (88 % vs. 65 %) and better ability to identify multigland disease (85 % vs. 25 %) [38–40].

Bilateral neck exploration without preoperative localization has long been considered the "gold standard" for surgical treatment of primary hyperparathyroidism [37]. The advent of reliable localization studies led to the development of minimally invasive parathyroid surgery and has radically changed the practice patterns over the last decades. Currently, MIP is the preferred approach for primary hyperparathyroidism when a single adenoma can be localized preoperatively, with surgeons increasingly adopting this approach over bilateral exploration [41, 42]. Minimally invasive parathyroidectomy is based on the excision of a single, well-localized parathyroid adenoma and is applicable to 90 % of the patients presenting

with sporadic primary hyperparathyroidism [43]. In addition to the localization studies, intraoperative parathyroid hormone monitoring (IOPTH) plays a role in identifying patients who may need a bilateral exploration. The main purpose of IOPTH is to identify patients with multigland disease—which account for 5–15 % of the patients [13]—during the course of the operation, In the presence of multigland disease, the sensitivity of Sestamibi drops from 97 to 61 % and the specificity from 93 to 84 % [44]. The "Miami" criteria are defined as IOPTH drop of ≥50 % from baseline at 10–15 min post-excision [45], with most experts agreeing that the post-excision IOPTH should be also be within normal limits [46]. If these criteria are not met after the resection of the suspected adenoma, further exploration is warranted. Multiple series have documented a slight increase in biochemical cure rate with the use of IOPTH from 95–97.5 to 97–99 % [12, 43, 47–50], although this difference has failed to reach statistical significance in any of the series.

At this stage, the decision of bilateral neck exploration vs. MIPS greatly depends on the surgeon's preference and expertise, although recent evidence seems to support minimally invasive approaches. Randomized trials comparing both techniques—presented in Table 46.1—consistently show equivalent cure rates even at 5-years postoperatively [51]. In a similar fashion, surgical resection of parathyroid adenomas through an <2 cm incision has been associated with shorter operative time, decreased pain and length of hospital stay, and better cosmetic results [52].

Overall, the success rate of surgery for primary hyperparathyroidism ranges between 94 and 99 % [11, 12, 31, 32, 35, 50, 53]. However, these outcomes must be interpreted cautiously, as most series come from high-volume, expert surgeons in centers with access to high-quality imaging and perioperative support [37], and may not accurately reflect surgical outcomes in less experienced hands. Worldwide, most parathyroid surgery is not performed by high-volume surgeons. This is also the case in the United States, where 78 % of the parathyroidectomies are performed by surgeons for whom endocrine case volume accounts for less than 25 % of their practice [54]. Several studies have suggested that surgeon's expertise and case volume is associated with better outcomes. In a study including 159 revision parathyroidectomies, Chen et al. [55] compared the surgical volume of the centers performing the initial failed operations and concluded that patients who underwent their initial procedure at low-volume centers (<50 parathyroidectomies/year) had almost a sevenfold increase in preventable operative failure, defined as missing an adenoma in a normal anatomical location. Similarly, a study based on the Scandinavian national registry comparing outcomes between high- and low-volume centers found biochemical cure rates of 90 % for endocrine surgery centers, 76 % for general surgery clinics, and only 70 % for centers performing less than 10 cases/year [56].

Invariably, the reasons for surgical failure include missing a single adenoma and failure to identify multigland disease. While preoperative localization studies collectively represent a major advance in the field, no technique can replace a thorough understanding of the role that embryology plays in the genesis of parathyroid adenomas. Every parathyroid surgeon should be able to perform a bilateral neck exploration and directly "look" for a missing adenoma in the most common locations. The superior parathyroid glands arise from the fourth branchial arch and have a relatively constant location, in the posterior aspect of the superior thyroid pole, adjacent to the cricothyroid junction and recurrent laryngeal nerve [34]. The inferior parathyroid glands arise from the third branchial arch and descent towards the thymus; while they are routinely located at the level of the inferior thyroid pole, they can be in any location within their embryological path. As such, their location is much more variable. A nomenclature system that uses mnemonic associations provides an easy way for uninitiated parathyroid surgeons to systematically explore common sites where adenomas could be missed [30] (Fig. 46.4).

Table 46.1 Outcomes of randomized trials comparing minimally invasive parathyroidectomy with bilateral neck exploration Callender et al. [37]

Authors	No. of patients	Randomized group (no.)	Results
Slepavicius [83]	48	MIP (24), BNE (24)	No difference in OR time, cosmesis at ≥1 year, or cure rate (100 % in both arms); less pain, better cosmesis at <1 year in MIP group; lower cost in BNE group
Miccoli [84]	40	Video-assisted MIP (20), endoscopic BNE (20)	No difference in OR time, complications (none), cure rate (95 % MIP, 100 % BNE); 3 BNE patients with single adenoma had additional "unnecessary" glands removed
Aarum [85]	100	MIP (50), BNE (50)	No difference in cure rate (96 % MIP, 94 % BNE); cost 21 % higher for MIP group; >50 % of MIP group actually underwent bilateral exploration
Sozio [86]	69	Radio-guided MIP (34), BNE (35)	No difference in cure rate (100 % in both arms); shorter OR time, LOS, and recovery time in MIP group
Bergenfelz [87]	50	MIP (25), BNE (25)	No difference in cure rate (96 % MIP, 100 % BNE); shorter OR time, less short-term hypocalcemia in MIP group
Bergenfelz [13] and Westerdahl & Bergenfelz [51]	91	Initial study: MIP (47), BNE (44); 5-years follow-up: MIP (38), BNE (33)	No difference in cost, temporary nerve palsy (2 MIP, 1 BNE), short-term cure rate (98 % in both arms), long-term cure rate at 5 years (89 % MIP, 94 % BNE); shorter OR time, less short-term hypocalcemia, less early severe symptomatic hypocalcemia, less long-term hypocalcemia in MIP group; 1 BNE patient with single adenoma still dependent on calcium/calcitriol at 5 years
Miccoli [88]	38	Video-assisted MIP (20), BNE (18)	No difference in cure rate (100 % in both arms); shorter OR time, less pain, better cosmesis in MIP group; no complications in BNE group vs. 1 RLN palsy in MIP group

BNE bilateral neck exploration, *LOS* length of stay, *MIP* minimally invasive parathyroidectomy, *OR* operating room, *RLN* recurrent laryngeal nerve

Reoperative parathyroid surgery is challenging and should be reserved for experienced surgeons in high-volume centers. Cure rates following reoperative parathyroidectomy are significantly lower than for primary surgery, ranging from 83 to 96.8 % [5, 57–59], and reoperative parathyroidectomy is associated with a higher complication rate [2–5]. Reoperations are also significantly more expensive, with a cost that roughly doubles that of the initial surgery [60]. As the risk/benefit balance significantly differs from the initial parathyroidectomy, candidates for reoperative surgery should be carefully evaluated. In these cases multiple localization studies are routinely performed looking for concordant findings which suggest an area of "high probability" to identify the adenoma. With localization protocols currently available, blind neck re-explorations should virtually never be required [37]. Anatomically, the missed adenomas will almost invariable be located along the embryological path of descent of the parathyroids. This is demonstrated in Fig. 46.5 which shows the anatomical location of missed adenomas in a series of 130 reoperative parathyroidectomies [61]. Technical advances will continue to impact

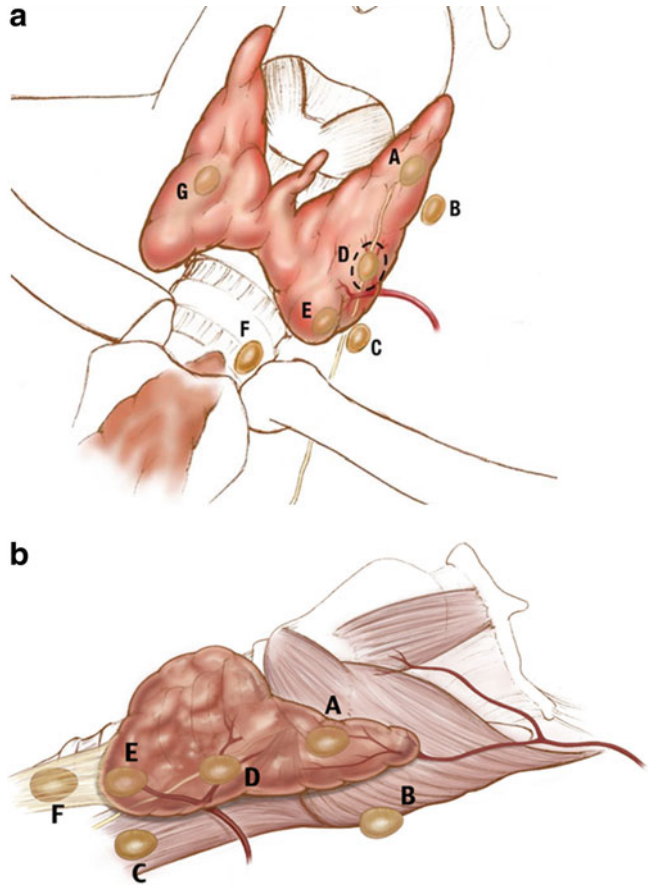

Fig. 46.4 (**a**) The "Perrier" classification; common locations of parathyroid adenomas Moreno et al. [30]. Type A: Adherent to the posterior thyroid parenchyma. A type A gland is in the accepted, expected location of a normal parathyroid gland. Type B: Behind the thyroid parenchyma. A type B gland is exophytic to the thyroid parenchyma and lies in the tracheoesophageal groove. Type C: Caudal to the thyroid parenchyma, in the tracheoesophageal groove. A type C gland is more inferior than a type B gland on lateral images and located inferior to the inferior pole of the thyroid (**c**loser to the **c**lavicle). Type D: Directly over the recurrent laryngeal nerve at the level of the inferior thyroid vessels. The dissection may be difficult because a type D gland is **d**angerously close to the recurrent laryngeal nerve. Type E: Located in the internal aspect of the inferior pole of the thyroid. A type E gland is in a location that is more superficial in an anterior–posterior plane than the recurrent laryngeal nerve. It is the **e**asiest to resect. Type F: "Fallen" into the thyrothymic ligament, below the inferior pole of the thyroid in a pretracheal plane. A type F gland is frequently referred to as an ectopic gland, and its resection usually involves transcervical delivery of the thyrothymic ligament or superior portion of the thymus. Type G: True intrathyroidal gland location. (**b**) Common location of parathyroid adenomas, lateral view

the management these patients. MRI-based, real-time intraoperative localization has been successfully tested in a small cohort of patients [62]. This, and similar techniques, will further add to the surgical armamentarium in the treatment of persistent and recurrent hyperparathyroidism.

Conversion to Bilateral Neck Exploration

In the context of minimally invasive surgery, conversion to bilateral exploration must not be viewed as a complication, but rather as part of

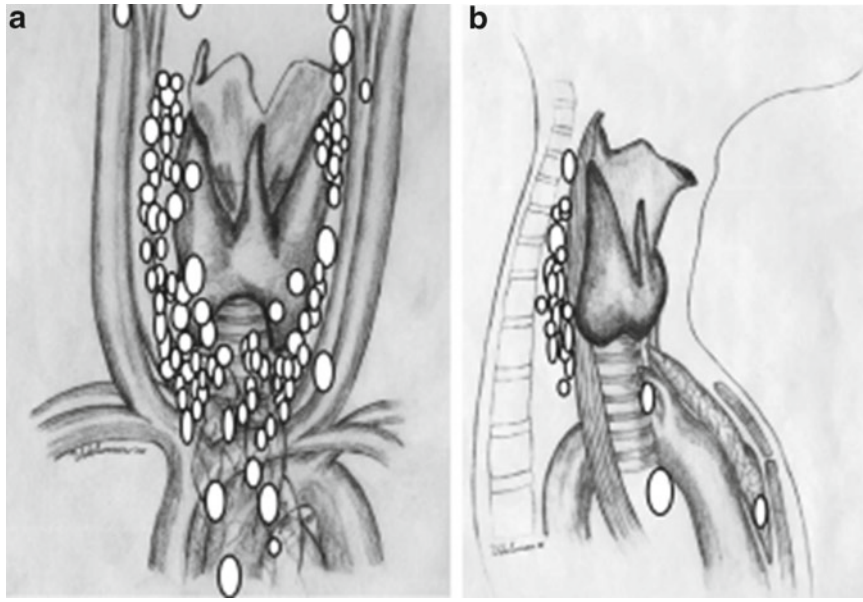

Fig. 46.5 The locations of parathyroid glands identified during reoperative parathyroid surgery are illustrated, including (**a**) an anterior–posterior view and (**b**) a lateral view Udelsman et al. [61]

a surgical continuum in an attempt to achieve biochemical cure. Failing to identify an abnormal parathyroid gland, or an insufficient drop in IOPTH following the resection of the suspected adenoma are probably the most common factors leading to the decision to convert from a minimally invasive approach. Other factors may also lead to the decision to convert to bilateral neck exploration, as reported by Norman et al. in a prospective series of 3000 consecutive patients. In this study, the authors identified the following intraoperative findings leading to open exploration: involvement of the recurrent laryngeal nerve, contralateral thyroid disease discovered, extensive scar tissue, abnormal ipsilateral gland, failure to identify ipsilateral gland and insufficient parathyroid hormone reduction [63]. Overall, there are many situations in which converting to bilateral neck exploration represents the most sensible approach and reflects appropriate surgical judgment. It is important for the surgeon to disclose the limitations of minimally invasive techniques, and to discuss the potential need for bilateral exploration in all cases.

Neck Hematoma

Hematomas of the central compartment are most commonly associated with thyroid surgery, but this complication may present after parathyroidectomy, although with a very low incidence. In a study comparing bilateral cervical exploration vs. MIPS, 0.2 % of the patients presented with hematoma after open approach while 0.8 % had a hematoma after MIPS [12]. Udelsman reports a 0.2 % incidence in a cohort of 1,650 consecutive patients [14] while Miccoli describes a 0.27 % incidence in patients treated with video-assisted parathyroidectomy [11].

In spite of their rarity, tension hematomas of the central neck compartment represent a serious, and potentially life-threatening complication that is worth noting. Acute bleeding in a nondistensible surgical cavity significantly increases the pressure in the larynx and perilaryngeal structures. This leads to venous congestion of the airway, edema of the supraglottic structures, and neurapraxia of the RLN which results in bilateral vocal cord paralysis. Patients present with noisy breathing or laryngeal stridor,

and characteristically adopt the tripod position trying to alleviate the pressure over the airway. A high index of suspicion is necessary as the diagnosis is based on clinical findings and patients can deteriorate rapidly. As early as the diagnosis is suspected, the surgical incision must be reopened to evacuate the hematoma. This maneuver usually alleviate the symptoms and stabilizes patient enough to proceed with a formal neck exploration.

Wound Infection

Overall, the risk of wound infection is extremely low. Parathyroid surgery is considered a clean surgery, so the wound infection rate should not exceed 1 %. A recent study of 776 patients undergoing parathyroidectomy reports a 0.3 % incidence of postoperative wound infection [64]. Like any elective surgery, routine, single-dose antibiotic prophylaxis should be used for all patients.

Adverse Scarring

In general, parathyroidectomy incisions are nearly invisible when fully healed. However, just like in any surgical procedure, there is low risk of adverse scarring that should always be disclosed to the patient. African Americans and patients with history of keloids or exuberant scars should be approached cautiously. A good practice is to ask the patient to reveal previous surgical scars to anticipate potential wound complications. Intraoperatively, the incision should be placed in a skin crease if at all possible. Care must be exercised with skin retraction, particularly in small incisions that provide limited exposure. Excessive retraction traumatizes the skin edges, leaving a short but noticeable scar in the neck. If the exposure is insufficient, is better to extend the incision than to risk an unsightly scar derived from excessive retraction. If a keloid scar is identified postoperatively, compression therapy, and intralesional corticosteroids should be initiated as early as possible.

Methylene Blue Toxicity

Intravenous administration of methylene blue has been used to identify abnormal parathyroid glands in patients with primary hyperparathyroidism. In a recent series of almost 100 patients, intravenous methylene blue appropriately stained close to 80 % of the glands [33]. The use of methylene blue has been associated with serotonin syndrome, a rare form of encephalopathy most frequent in patients under treatment with selective serotonin reuptake inhibitors (SSRIs) drugs [65]. This condition is characterized by autonomic, neurological, and neuromuscular instability presenting in the postoperative period. Clinical suspicion is important to recognize this condition. The treatment usually involves support measures as most cases resolve spontaneously within days. Since depressive symptoms are common in patients with primary hyperparathyroidism, use of SSRI should be directly inquired and the use of methylene blue should be avoided in these patients [66].

Parathyromatosis

Parathyromatosis is a rare iatrogenic complication that results from the rupture of an adenomatous gland. This causes seeding of hyperfunctioning parathyroid cells and subsequent development of miliary nodules in the exposed soft tissues. When present, this condition is only identified intraoperatively, as the nodules are too small to be detected in preoperative imaging or localization studies [67]. Given its etiology, parathyromatosis is only identified in the context of reoperative parathyroid surgery, and has been described to be more common in patients treated for secondary hyperparathyroidism [68]. From the surgeon's perspective it poses an extremely challenging scenario as the only option for cure is en-bloc resection of the involved tissues, which in most cases only serves as a debulking. Unfortunately, most patients will require long-term medical management after the surgical attempt. Since this an avoidable complication, parathyroid surgeons should be cognizant of the condition and exercise meticulous surgical technique at all times.

Pneumothorax

Pneumothorax is a rare complication of parathyroidectomy. In a report of 4 patients who developed pneumothorax after MIP, extreme neck hyperextension was identified as the common denominator for the cohort [69]. The authors also identified other factors that could place patients at risk, including dissection in the superior mediastinum, traction on the thyrothymic ligament, and a low-lying inferior parathyroid gland [69]. Another report—also in patients undergoing MIP—identified mediastinal adenomas and history of emphysema as potential risk factors [70]. Pneumothorax has also been reported in patients undergoing bilateral neck exploration; Low et al. report a single case in a series of 766 open procedures (0.1%) [29]. Regardless of the surgical approach, care must be exercised when addressing lesions located low in the neck or in the mediastinum, as the proximity of the pleural apices appears to increase the risk of this complication.

Hungry Bone Syndrome

Hungry bone syndrome (HBS) is an uncommon but potentially devastating complication of parathyroidectomy in the context of primary hyperparathyroidism. It is defined as a profound (serum calcium <2.1 mmol/l), prolonged (beyond the 4th postoperative day) and symptomatic [71] hypocalcemia, commonly associated with hypophosphatemia and hypomagnesaemia, that is observed almost exclusively in patients with severe hyperparathyroidism and high bone turnover. This complication is almost exclusively seen in patients with secondary and tertiary hyperparathyroidism. The etiology of HBS is the rapid incorporation of calcium into bone following an abrupt decline in serum PTH levels and associated osteoclastic bone resorption. In these cases, there is a decrease in activation of new bone remodeling sites in the context of a persistently elevated osteoblastic activity, leading to a rapid increase in bone mass. From the clinical perspective, it is important to differentiate this condition from other causes of postoperative hypocalcemia in patients with primary hyperparathyroidism. In most of these patients, the drop in serum calcium is mild, self-limited, and maximal between the second and fourth postoperative days [72, 73]. Devascularization, surgical trauma or just long-term suppression of the remaining parathyroid glands are plausible causes for prolonged postoperative hypocalcemia; however, in these cases the hypocalcemia will typically not be as severe, and patients will lack the characteristic musculoskeletal manifestations observed in patients with HBS such as *osteitis fibrosa cystica* and *brown tumors*. These bony defects are heraldic of increased osteoclastic activity and their presence should be acknowledged by the clinician prior to surgery.

Patients considered at-risk for developing this condition include those with long-standing disease, high PTH levels [74, 75], large adenomas [76], older age [74], altered bone density or bone pain [77], elevated serum alkaline phosphatase [74], and low levels of vitamin-D [74, 78]. In a recent systematic literature review, Witteveen et al. reports that the incidence of HBS is 25–90% in patients with any radiological evidence of parathyroid disease vs. 0–6% in patients without evidence of skeletal involvement [79]. In terms of biochemical risk stratification, several markers have been identified as potential predictors for the development of this condition (Table 46.2). These tests should be requested and interpreted in the context of a comprehensive preoperative evaluation of patients with secondary and tertiary hyperparathyroidism.

The primary treatment of HBS is close monitoring and aggressive supplementation of serum calcium, commonly requiring doses of 6–12 g. of elemental calcium per day [80]. Routinely, intravenous supplementation will be first and subsequently transitioned to oral supplementation. Vitamin-D analogs have been a critical addition to armamentarium for the management of severe hypocalcemia, these drugs should be started promptly and the dose should be escalated liberally. In a similar fashion, serum magnesium should be closely monitored and properly replenished.

Bisphosphonates are part of the pharmacological arsenal against the osteoclast-mediated

Table 46.2 Preoperative laboratory data in patients with primary hyperparathyroidism who developed HBS following parathyroidectomy compared with those who did not Witteveen et al. [79]

Laboratory investigation	Authors	Patients who developed HBS	Patients who did not develop HBS	*P* value
s-Calcium (mmol/l)	Brasier & Nussbaum [74]	3.00±0.05	2.88±0.03	<0.05
	Spiegel et al. [89]	3.25±0.05	3.00±0.03	<0.001
	Heath et al. [78]	3.94±0.38	2.95±0.15	<0.01
	Lee et al. [75]	3.00±0.1	3.00±0.08	0.7
s-PTH (pmol/l)	Brasier & Nussbaum [74]	10.2±2.00	5.7±0.3	<0.05
	Lee et al. [75]	30.7±10	32.9±6	0.2
s-Alkaline phosphatase (U/l)	Brasier & Nussbaum [74]	68±15	38±2	<0.05
	Heath et al. [78]	51±37	12±6	<0.01
	Lee et al. [75]	248±48	169±31	0.1
s-Magnesium (mEq/l)	Brasier & Nussbaum [74]	1.5±0.1	1.7±0.04	<0.001
s-Albumin (g/dl)	Brasier & Nussbaum [74]	3.9±0.1	4.3±0.04	<0.001

bone loss that characterizes several conditions; in light of the common pathogenic pathway with HBS, these agents have been used to prevent the development of this complication. In this regards, several authors have reported a both decreased severity and duration of HBS among patients treated with this family of drugs prior to their surgery [81, 82].

Summary

Complications arising from parathyroid surgery are similar to those from the other chief surgery of the central neck, thyroidectomy. Since in many cases, the patients are not highly symptomatic from their hyperparathyroidism, it is very important to mitigate risks and avoid complications. A unique complication of parathyroid surgery which raises the likelihood of future complications, is the failure to find the offending parathyroid gland(s) which sets the stage for a revision operation.

Society Guidelines: N/A

Best Practices: N/A

Expert Opinion

Although the complications for parathyroid surgery are largely shared with thyroid surgery, the potential most potentially devastating complication is failure to manage the hyperparathyroidism leading to the need for revision surgery.

References

1. Udelsman R, Akerstrom G, Biagini C, et al. The surgical management of asymptomatic primary hyperparathyroidism: proceedings of the Fourth International Workshop. J Clin Endocrinol Metab. 2014;99(10):3595–606. **Clinical Review; Level 2; Grade A–B**.
2. Hasse C, Sitter H, Brune M, Wollenteit I, Nies C, Rothmund M. Quality of life and patient satisfaction after reoperation for primary hyperparathyroidism: analysis of long-term results. World J Surg. 2002;26(8):1029–36. **Clinical Review; Level 2; Grade A–B**.
3. Karakas E, Muller HH, Schlosshauer T, Rothmund M, Bartsch DK. Reoperations for primary hyperparathyroidism—improvement of outcome over two decades. Langenbecks Arch Surg. 2013;398(1):99–106. **Clinical Review; Level 2; Grade A–B**.

4. van Heerden JA, Grant CS. Surgical treatment of primary hyperparathyroidism: an institutional perspective. World J Surg. 1991;15(6):688–92. **Population/ Obervational Study; Level 3; Grade A–B**.
5. Wachtel H, Cerullo I, Bartlett EK, Kelz RR, Karakousis GC, Fraker DL. What can we learn from intraoperative parathyroid hormone levels that do not drop appropriately? Ann Surg Oncol. 2015;22(6):1781–8. **Clinical Review; Level 3; Grade A–B**.
6. Morris LF, Zelada J, Wu B, Hahn TJ, Yeh MW. Parathyroid surgery in the elderly. Oncologist. 2010;15(12):1273–84. **Clinical Review; Level 3; Grade A–B**.
7. Chigot JP, Menegaux F, Achrafi H. Should primary hyperparathyroidism be treated surgically in elderly patients older than 75 years? Surgery. 1995;117(4):397–401. **Clinical Review; Level 3; Grade A–B**.
8. Irvin 3rd GL, Carneiro DM. "Limited" parathyroidectomy in geriatric patients. Ann Surg. 2001;233(5):612–6. **Clinical Review; Level 3; Grade A–B**.
9. Young VN, Osborne KM, Fleming MM, Flynn MB, Goldstein RE, Bumpous JM. Parathyroidectomy in the elderly population: does age really matter? Laryngoscope. 2010;120(2):247–52. **Clinical Review; Level 3; Grade A–B**.
10. Stack Jr BC, Bimston DN, Bodenner DL, et al. American Association of Clinical Endocrinologists and American College of Endocrinology disease state clinical review: postoperative hypoparathyroidism — definitions and management. Endocr Pract. 2015;21(6):674–85. **Clinical Review; Level 2; Grade B**.
11. Miccoli P, Berti P, Materazzi G, Massi M, Picone A, Minuto MN. Results of video-assisted parathyroidectomy: single institution's six-year experience. World J Surg. 2004;28(12):1216–8. **Population/ Observational Study; Level 3; Grade B**.
12. Udelsman R. Six hundred fifty-six consecutive explorations for primary hyperparathyroidism. Ann Surg. 2002;235(5):665–70. discussion 670–662. **Population/Observational Study; Level 3; Grade B**.
13. Bergenfelz A, Lindblom P, Tibblin S, Westerdahl J. Unilateral versus bilateral neck exploration for primary hyperparathyroidism: a prospective randomized controlled trial. Ann Surg. 2002;236(5):543–51. **Clinical Investigation; Level 1; Grade B**.
14. Udelsman R, Lin Z, Donovan P. The superiority of minimally invasive parathyroidectomy based on 1650 consecutive patients with primary hyperparathyroidism. Ann Surg. 2011;253(3):585–91. **Clinical Investigation; Level 1; Grade B**.
15. Shaha AR, Jaffe BM. Parathyroid preservation during thyroid surgery. Am J Otolaryngol. 1998;19(2):113–7. **Clinical Investigation; Level 3; Grade A–B**.
16. Wingert DJ, Friesen SR, Iliopoulos JI, Pierce GE, Thomas JH, Hermreck AS. Post-thyroidectomy hypocalcemia. Incidence and risk factors. Am J Surg. 1986;152(6):606–10. **Population/Observational Study; Level 3; Grade B**.
17. Makay O, Icoz G, Yilmaz M, Akyildiz M, Yetkin E. The recurrent laryngeal nerve and the inferior thyroid artery — anatomical variations during surgery. Langenbecks Arch Surg. 2008;393(5):681–5. **Population/Observational Study; Level 3; Grade A**.
18. Moreau S, Goullet de Rugy M, Babin E, Salame E, Delmas P, Valdazo A. The recurrent laryngeal nerve: related vascular anatomy. Laryngoscope. 1998;108(9):1351–3. **Population/Observational Study; Level 3; Grade A**.
19. Beneragama T, Serpell JW. Extralaryngeal bifurcation of the recurrent laryngeal nerve: a common variation. ANZ J Surg. 2006;76(10):928–31. **Population/ Observational Study; Level 3; Grade A**.
20. Cernea CR, Hojaij FC, De Carlucci Jr D, et al. Recurrent laryngeal nerve: a plexus rather than a nerve? Arch Otolaryngol. 2009;135(11):1098–102. **Population/Observational Study; Level 3; Grade B**.
21. Serpell JW, Yeung MJ, Grodski S. The motor fibers of the recurrent laryngeal nerve are located in the anterior extralaryngeal branch. Ann Surg. 2009;249(4):648–52. **Population/Observational Study; Level 3; Grade B**.
22. Chandrasekhar SS, Randolph GW, Seidman MD, et al. Clinical practice guideline: improving voice outcomes after thyroid surgery. Otolaryngology. 2013;148(6 Suppl):S1–37. **Clinical Review; Level 2; Grade A–B**.
23. Sancho JJ, Pascual-Damieta M, Pereira JA, Carrera MJ, Fontane J, Sitges-Serra A. Risk factors for transient vocal cord palsy after thyroidectomy. Br J Surg. 2008;95(8):961–7. **Population/Observational Study; Level 3; Grade B**.
24. Genther DJ, Kandil EH, Noureldine SI, Tufano RP. Correlation of final evoked potential amplitudes on intraoperative electromyography of the recurrent laryngeal nerve with immediate postoperative vocal fold function after thyroid and parathyroid surgery. JAMA Otolaryngol. 2014;140(2):124–8. **Population/ Observational Study; Level 3; Grade B**.
25. Netterville JL, Aly A, Ossoff RH. Evaluation and treatment of complications of thyroid and parathyroid surgery. Otolaryngol Clin North Am. 1990;23(3):529–52. **Population/Observational Study; Level 3; Grade B**.
26. Srinivasan V, Premachandra DJ. Non-recurrent laryngeal nerve: identification during thyroid surgery. Oral J Oto-rhino Laryngol. 1997;59(1):57–9. **Population/ Observational Study; Level 3; Grade B**.
27. Cannon CR. The anomaly of nonrecurrent laryngeal nerve: identification and management. Otolaryngology. 1999;120(5):769–71. **Population/ Observational Study; Level 3; Grade B**.
28. Fellmer PT, Bohner H, Wolf A, Roher HD, Goretzki PE. A left nonrecurrent inferior laryngeal nerve in a patient with right-sided aorta, truncus arteriosus communis, and an aberrant left innominate artery. Thyroid.

2008;18(6):647–9. **Clinical Review; Level 2; Grade A–B**.
29. Low RA, Katz AD. Parathyroidectomy via bilateral cervical exploration: a retrospective review of 866 cases. Head Neck. 1998;20(7):583–7. **Clinical Investigation; Level 3; Grade A–B**.
30. Moreno MA, Callender GG, Woodburn K, et al. Common locations of parathyroid adenomas. Ann Surg Oncol. 2011;18(4):1047–51. **Population/Observational Study; Level 3; Grade B**.
31. Karakas E, Schneider R, Rothmund M, Bartsch DK, Schlosser K. Initial surgery for benign primary hyperparathyroidism: an analysis of 1,300 patients in a teaching hospital. World J Surg. 2014;38(8):2011–8. **Population/Observational Study; Level 3; Grade B**.
32. Allendorf J, DiGorgi M, Spanknebel K, Inabnet W, Chabot J, Logerfo P. 1112 consecutive bilateral neck explorations for primary hyperparathyroidism. World J Surg. 2007;31(11):2075–80. **Population/Observational Study; Level 3; Grade B**.
33. Bewick J, Pfleiderer A. The value and role of low dose methylene blue in the surgical management of hyperparathyroidism. Ann R Coll Surg Engl. 2014;96(7):526–9. **Clinical Investigation; Level 3; Grade A–B**.
34. Rice DH. Surgery of the parathyroid glands. Otolaryngol Clin North Am. 1996;29(4):693–9. **Clinical Review; Level 3; Grade A–B**.
35. Shaha AR, Jaffe BM. Cervical exploration for primary hyperparathyroidism. J Surg Oncol. 1993;52(1):14–7. **Clinical Review; Level 3; Grade A–B**.
36. Sofferman RA, Standage J, Tang ME. Minimal-access parathyroid surgery using intraoperative parathyroid hormone assay. Laryngoscope. 1998;108(10):1497–503. **Clinical Investigation; Level 3; Grade A–B**.
37. Callender GG, Udelsman R. Surgery for primary hyperparathyroidism. Cancer. 2014;120(23):3602–16. **Clinical Review; Level 3; Grade A–B**.
38. Kettle AG, O'Doherty MJ. Parathyroid imaging: how good is it and how should it be done? Semin Nucl Med. 2006;36(3):206–11. **Clinical Review; Level 3; Grade A–B**.
39. Rodgers SE, Hunter GJ, Hamberg LM, et al. Improved preoperative planning for directed parathyroidectomy with 4-dimensional computed tomography. Surgery. 2006;140(6):932–40. discussion 940–931. **Clinical Investigation; Level 3; Grade A–B**.
40. Starker LF, Mahajan A, Bjorklund P, Sze G, Udelsman R, Carling T. 4D parathyroid CT as the initial localization study for patients with de novo primary hyperparathyroidism. Ann Surg Oncol. 2011;18(6):1723–8. **Clinical Investigation; Level 3; Grade A–B**.
41. Carling T, Udelsman R. Focused approach to parathyroidectomy. World J Surg. 2008;32(7):1512–7. **Clinical Review; Level 3; Grade A–B**.
42. Sackett WR, Barraclough B, Reeve TS, Delbridge LW. Worldwide trends in the surgical treatment of primary hyperparathyroidism in the era of minimally invasive parathyroidectomy. Arch Surg. 2002;137(9):1055–9. **Population/Observational Study; Level 3; Grade B**.
43. Morris LF, Zanocco K, Ituarte PH, et al. The value of intraoperative parathyroid hormone monitoring in localized primary hyperparathyroidism: a cost analysis. Ann Surg Oncol. 2010;17(3):679–85. **Clinical Investigation; Level 3; Grade A–B**.
44. Nichols KJ, Tomas MB, Tronco GG, Palestro CJ. Sestamibi parathyroid scintigraphy in multigland disease. Nucl Med Commun. 2012;33(1):43–50. **Clinical Investigation; Level 3; Grade A–B**.
45. Irvin 3rd GL, Dembrow VD, Prudhomme DL. Operative monitoring of parathyroid gland hyperfunction. Am J Surg. 1991;162(4):299–302. **Clinical Investigation; Level 3; Grade A–B**.
46. Richards ML, Thompson GB, Farley DR, Grant CS. An optimal algorithm for intraoperative parathyroid hormone monitoring. Arch Surg. 2011;146(3):280–5. **Clinical Investigation; Level 3; Grade A–B**.
47. Arici C, Cheah WK, Ituarte PH, et al. Can localization studies be used to direct focused parathyroid operations? Surgery. 2001;129(6):720–9. **Clinical Investigation; Level 3; Grade A–B**.
48. Chen H, Pruhs Z, Starling JR, Mack E. Intraoperative parathyroid hormone testing improves cure rates in patients undergoing minimally invasive parathyroidectomy. Surgery. 2005;138(4):583–7. discussion 587–590. **Clinical Investigation; Level 3; Grade A–B**.
49. Mihai R, Palazzo FF, Gleeson FV, Sadler GP. Minimally invasive parathyroidectomy without intraoperative parathyroid hormone monitoring in patients with primary hyperparathyroidism. Br J Surg. 2007;94(1):42–7. **Clinical Investigation; Level 3; Grade A–B**.
50. Pang T, Stalberg P, Sidhu S, et al. Minimally invasive parathyroidectomy using the lateral focused mini-incision technique without intraoperative parathyroid hormone monitoring. Br J Surg. 2007;94(3):315–9. **Clinical Investigation; Level 3; Grade A–B**.
51. Westerdahl J, Bergenfelz A. Unilateral versus bilateral neck exploration for primary hyperparathyroidism: five-year follow-up of a randomized controlled trial. Ann Surg. 2007;246(6):976–80. discussion 980–971. **Clinical Investigation; Level 1; Grade B**.
52. Mihai R, Barczynski M, Iacobone M, Sitges-Serra A. Surgical strategy for sporadic primary hyperparathyroidism an evidence-based approach to surgical strategy, patient selection, surgical access, and reoperations. Langenbecks Arch Surg. 2009;394(5):785–98. **Clinical Review; Level 3; Grade A–B**.
53. Lew JI, Solorzano CC. Surgical management of primary hyperparathyroidism: state of the art. Surg Clin North Am. 2009;89(5):1205–25. **Clinical Review; Level 3; Grade A–B**.
54. Saunders BD, Wainess RM, Dimick JB, Doherty GM, Upchurch GR, Gauger PG. Who performs endocrine operations in the United States? Surgery. 2003;134(6):924–31. discussion 931. **Clinical Review; Level 3; Grade A–B**.

55. Chen H, Wang TS, Yen TW, et al. Operative failures after parathyroidectomy for hyperparathyroidism: the influence of surgical volume. Ann Surg. 2010;252(4):691–5. **Population/Observational Study; Level 3; Grade B**.
56. Malmaeus J, Granberg PO, Halvorsen J, Akerstrom G, Johansson H. Parathyroid surgery in Scandinavia. Acta Chir Scand. 1988;154(7–8):409–13. **Population/Observational Study; Level 3; Grade B**.
57. Cheung PS, Borgstrom A, Thompson NW. Strategy in reoperative surgery for hyperparathyroidism. Arch Surg. 1989;124(6):676–80. **Clinical Investigation; Level 3; Grade A–B**.
58. Granberg PO, Johansson G, Lindvall N, et al. Reoperation for primary hyperparathyroidism. Am J Surg. 1982;143(3):296–300. **Clinical Investigation; Level 3; Grade A–B**.
59. Jaskowiak N, Norton JA, Alexander HR, et al. A prospective trial evaluating a standard approach to reoperation for missed parathyroid adenoma. Ann Surg. 1996;224(3):308–20. discussion 320–301. **Clinical Investigation; Level 2; Grade B**.
60. Doherty GM, Weber B, Norton JA. Cost of unsuccessful surgery for primary hyperparathyroidism. Surgery. 1994;116(6):954–7. discussion 957–958. **Clinical Investigation; Level 3; Grade A–B**.
61. Udelsman R, Donovan PI. Remedial parathyroid surgery: changing trends in 130 consecutive cases. Ann Surg. 2006;244(3):471–9. **Population/Observational Study; Level 3; Grade B**.
62. Jayender J, Lee TC, Ruan DT. Real-time localization of parathyroid adenoma during parathyroidectomy. N Engl J Med. 2015;373(1):96–8. **Clinical Investigation; Level 3; Grade A–B**.
63. Norman J, Politz D. Prospective study in 3,000 consecutive parathyroid operations demonstrates 18 objective factors that influence the decision for unilateral versus bilateral surgical approach. J Am Coll Surg. 2010;211(2):244–9. **Clinical Investigation; Level 2; Grade B**.
64. Rajeev P, Sutaria R, Ezzat T, Mihai R, Sadler GP. Changing trends in thyroid and parathyroid surgery over the decade: is same-day discharge feasible in the United Kingdom? World J Surg. 2014;38(11):2825–30. **Population/Observational Study; Level 3; Grade B**.
65. Ng BK, Cameron AJ, Liang R, Rahman H. Serotonin syndrome following methylene blue infusion during parathyroidectomy: a case report and literature review. Can J Anaesth. 2008;55(1):36–41. **Clinical Investigation; Level 4**.
66. Shopes E, Gerard W, Baughman J. Methylene blue encephalopathy: a case report and review of published cases. AANA J. 2013;81(3):215–21. **Clinical Investigation; Level 4**.
67. Tublin ME, Yim JH, Carty SE. Recurrent hyperparathyroidism secondary to parathyromatosis: clinical and imaging findings. J Ultrasound Med. 2007;26(6):847–51. **Clinical Investigation; Level 4**.
68. Matsuoka S, Tominaga Y, Sato T, et al. Recurrent renal hyperparathyroidism caused by parathyromatosis. World J Surg. 2007;31(2):299–305. **Clinical Investigation; Level 4**.
69. Guerrero MA, Wray CJ, Kee SS, Frenzel JC, Perrier ND. Minimally invasive parathyroidectomy complicated by pneumothoraces: a report of 4 cases. J Surg Educ. 2007;64(2):101–7. discussion 113. **Clinical Investigation; Level 4**.
70. Slater B, Inabnet WB. Pneumothorax: an uncommon complication of minimally invasive parathyroidectomy. Surg Laparosc Endosc Percutan Tech. 2005;15(1):38–40. **Clinical Investigation; Level 4**.
71. Shoback D. Clinical practice. Hypoparathyroidism. N Engl J Med. 2008;359(4):391–403. **Clinical Review; Level 3; Grade A–B**.
72. Chia SH, Weisman RA, Tieu D, Kelly C, Dillmann WH, Orloff LA. Prospective study of perioperative factors predicting hypocalcemia after thyroid and parathyroid surgery. Arch Otolaryngol. 2006;132(1):41–5. **Population/Observational Study; Level 3; Grade B**.
73. Westerdahl J, Lindblom P, Valdemarsson S, Tibblin S, Bergenfelz A. Risk factors for postoperative hypocalcemia after surgery for primary hyperparathyroidism. Arch Surg. 2000;135(2):142–7. **Population/Observational Study; Level 3; Grade B**.
74. Brasier AR, Nussbaum SR. Hungry bone syndrome: clinical and biochemical predictors of its occurrence after parathyroid surgery. Am J Med. 1988;84(4):654–60. **Population/Observational Study; Level 3; Grade B**.
75. Lee IT, Sheu WH, Tu ST, Kuo SW, Pei D. Bisphosphonate pretreatment attenuates hungry bone syndrome postoperatively in subjects with primary hyperparathyroidism. J Bone Miner Metab. 2006;24(3):255–8. **Clinical Investigation; Level 4**.
76. Zamboni WA, Folse R. Adenoma weight: a predictor of transient hypocalcemia after parathyroidectomy. Am J Surg. 1986;152(6):611–5. **Clinical Investigation; Level 3; Grade A–B**.
77. Agarwal G, Mishra SK, Kar DK, et al. Recovery pattern of patients with osteitis fibrosa cystica in primary hyperparathyroidism after successful parathyroidectomy. Surgery. 2002;132(6):1075–83. discussion 1083–1075. **Population/Observational Study; Level 3; Grade B**.
78. Heath DA, Van't Hoff W, Barnes AD, Gray JG. Value of 1-alpha-hydroxy vitamin D3 in treatment of primary hyperparathyroidism before parathyroidectomy. Br Med J. 1979;1(6161):450–2. **Clinical Investigation; Level 3; Grade A–B**.
79. Witteveen JE, van Thiel S, Romijn JA, Hamdy NA. Hungry bone syndrome: still a challenge in the postoperative management of primary hyperparathyroidism: a systematic review of the literature. Eur J Endocrinol. 2013;168(3):R45–53. **Clinical Review; Level 3; Grade A–B**.

80. Corsello SM, Paragliola RM, Locantore P, et al. Post-surgery severe hypocalcemia in primary hyperparathyroidism preoperatively treated with zoledronic acid. Hormones. 2010;9(4):338–42. **Clinical Investigation; Level 3; Grade A–B**.
81. Graal MB, Wolffenbuttel BH. Consequences of long-term hyperparathyroidism. Neth J Med. 1998;53(1):37–42. **Clinical Review; Level 3; Grade A–B**.
82. Kumar A, Ralston SH. Bisphosphonates prevent the hungry bone syndrome. Nephron. 1996;74(4):729. **Clinical Review; Level 3; Grade A–B**.
83. Slepavicius A, Beisa V, Janusonis V, Strupas K. Focused versus conventional parathyroidectomy for primary hyperparathyroidism: a prospective, randomized, blinded trial. Langenbecks Arch Surg. 2008;393(5):659–66. **Clinical Investigation; Level 1; Grade A–B**.
84. Miccoli P, Berti P, Materazzi G, Ambrosini CE, Fregoli L, Donatini G. Endoscopic bilateral neck exploration versus quick intraoperative parathormone assay (qPTHa) during endoscopic parathyroidectomy: a prospective randomized trial. Surg Endosc. 2008;22(2):398–400. **Clinical Investigation; Level 1; Grade A–B**.
85. Aarum S, Nordenstrom J, Reihner E, et al. Operation for primary hyperparathyroidism: the new versus the old order. A randomised controlled trial of preoperative localisation. Scand J Surg. 2007;96(1):26–30. **Clinical Investigation; Level 1; Grade A–B**.
86. Sozio A, Schietroma M, Franchi L, Mazzotta C, Cappelli S, Amicucci G. Parathyroidectomy: bilateral exploration of the neck vs minimally invasive radioguided treatment. Minerva Chir. 2005;60(2):83–9. **Clinical Investigation; Level 3; Grade A–B**.
87. Bergenfelz A, Kanngiesser V, Zielke A, Nies C, Rothmund M. Conventional bilateral cervical exploration versus open minimally invasive parathyroidectomy under local anaesthesia for primary hyperparathyroidism. Br J Surg. 2005;92(2):190–7. **Clinical Investigation; Level 3; Grade A–B**.
88. Miccoli P, Bendinelli C, Berti P, Vignali E, Pinchera A, Marcocci C. Video-assisted versus conventional parathyroidectomy in primary hyperparathyroidism: a prospective randomized study. Surgery. 1999;126(6):1117–21. discussion 1121–1112. **Clinical Investigation; Level 3; Grade A–B**.
89. Spiegel AM, Marx SJ, Brennan MF, et al. Parathyroid function after parathyroidectomy: evaluation by measurement of urinary cAMP. Clin Endocrinol (Oxf). 1981;15(1):65–73. **Clinical Investigation; Level 3; Grade A–B**.